Computer-Aided Design of Radionuclide Sequestering Agents

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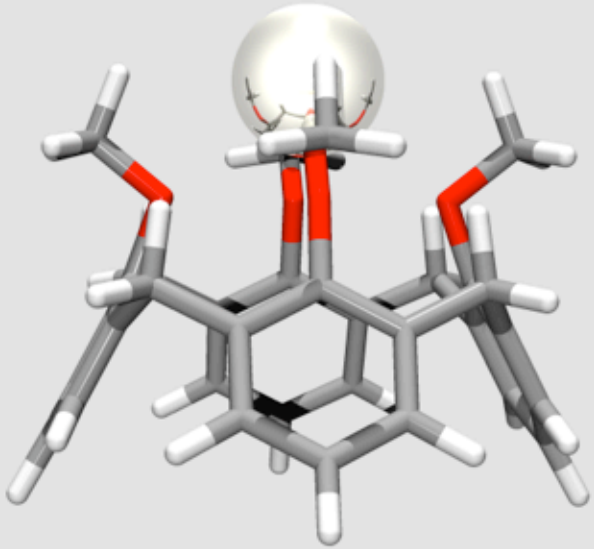
Motivation: recycle of spent nuclear fuel

- recovery of uranium and other actinides
- increase proliferation resistance
- reduce long-lived radionuclides in the waste
- reduce heat load on the waste
- reduce volume of waste going to repository



High End Computing for Nuclear Fission Science and Engineering
Salt Lake City, February 24, 2006

Office of Science
U.S. DEPARTMENT OF ENERGY

Pacific Northwest National Laboratory
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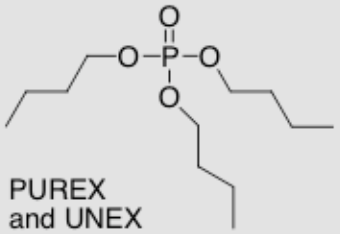
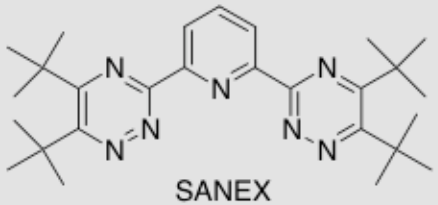
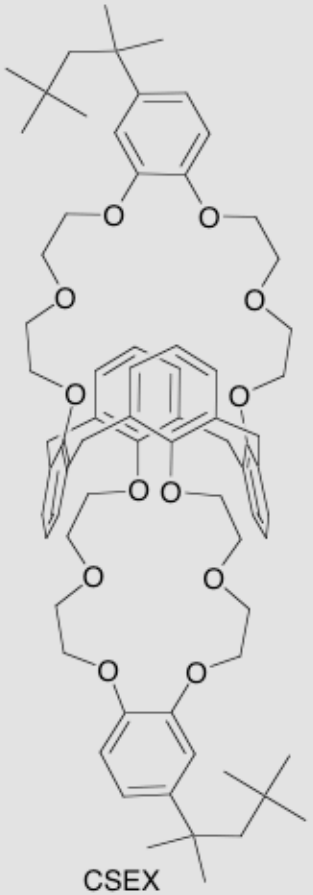
Sequestering agents used in radionuclide separations



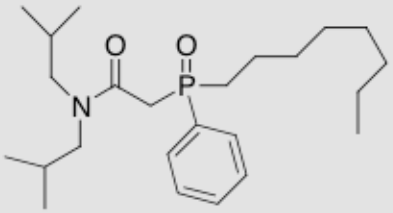
PUREX
and UNEX



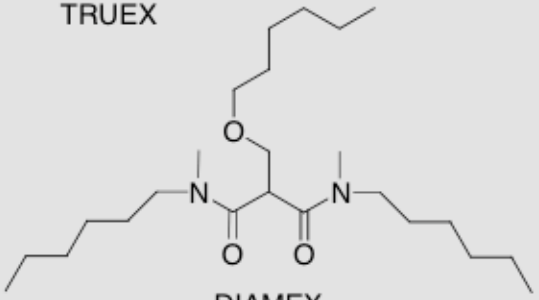
SANEX



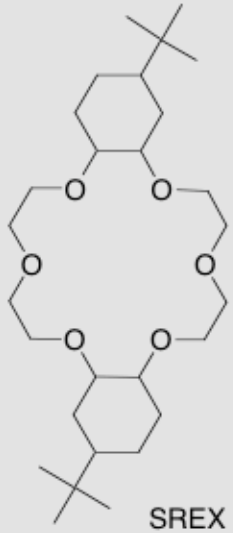
CSEX



TRUEX

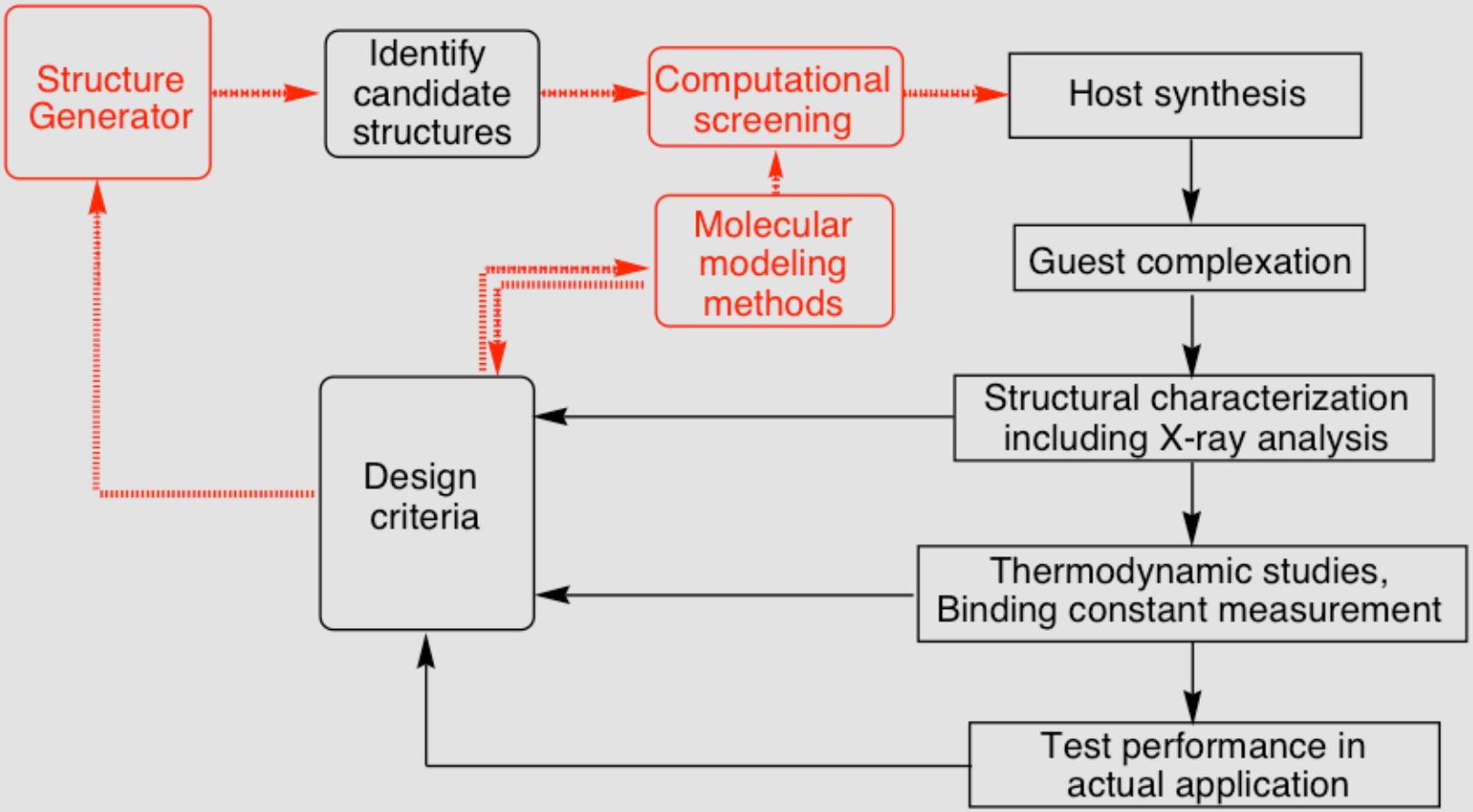


DIAMEX

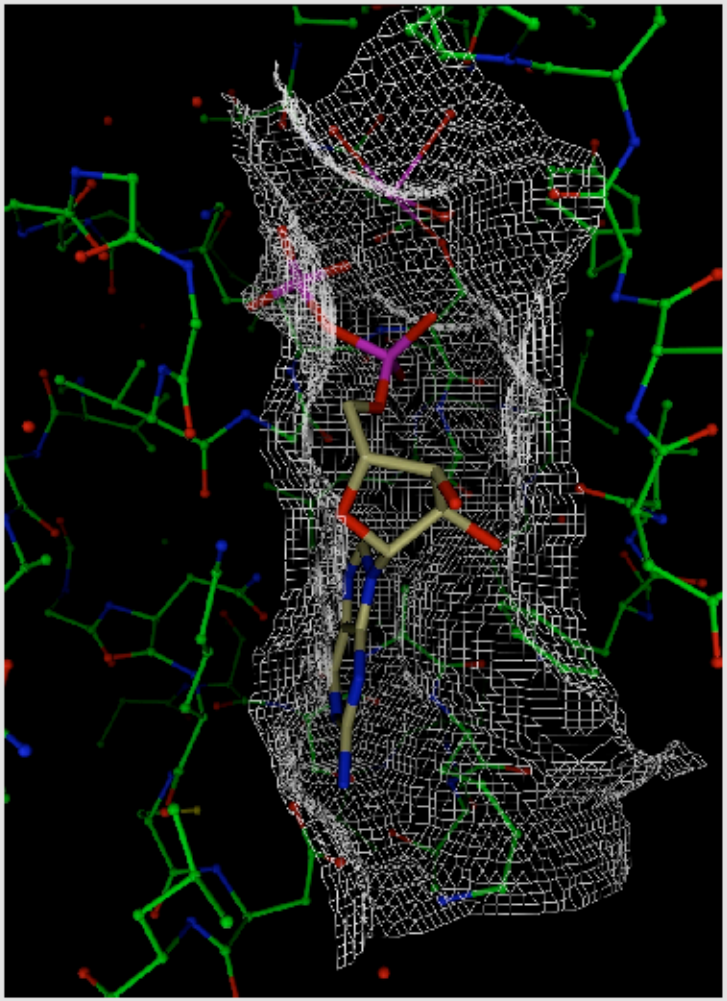


SREX

Computer-aided design cycle



De novo structure-based drug design



Step 1: Structural basis

- shape of host cavity
- H-bond regions
- hydrophobic regions

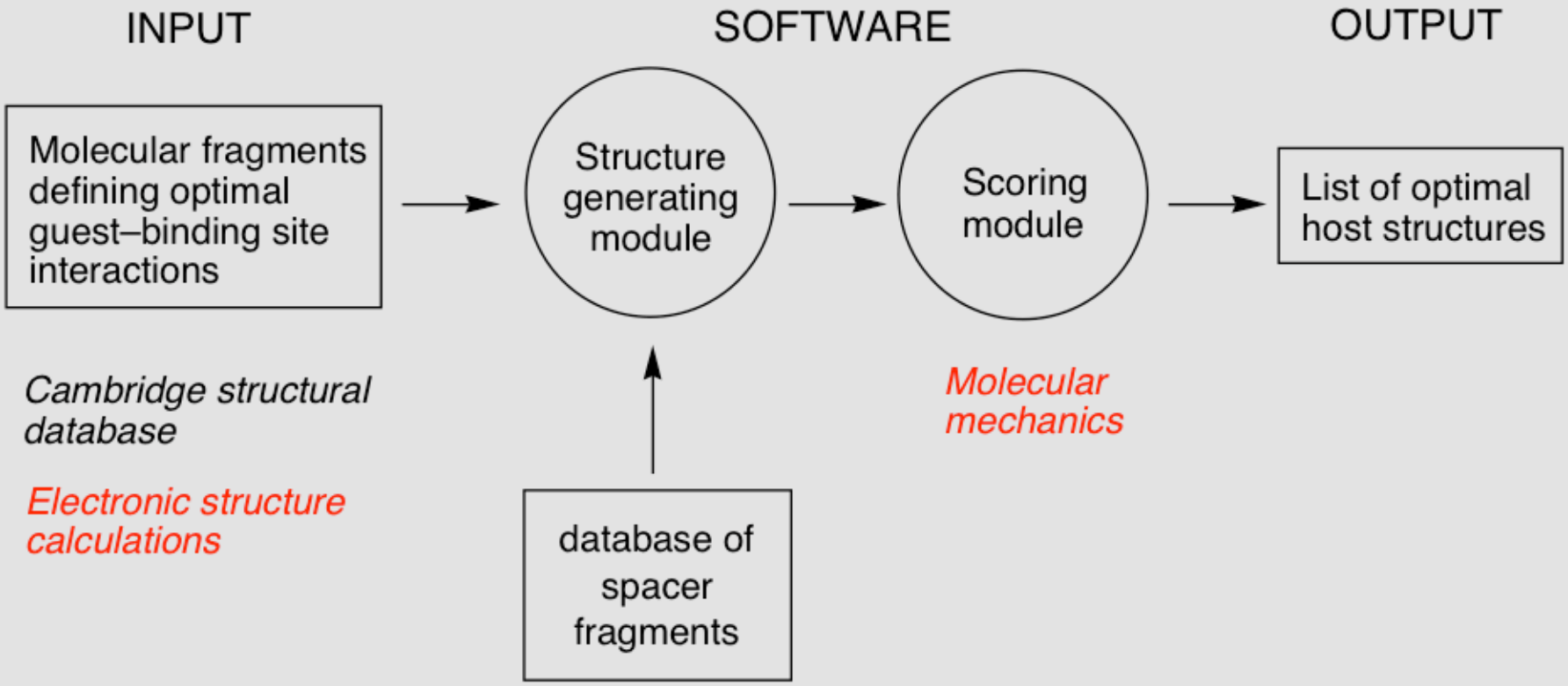
Step 2: Build candidate guests

- position functional groups
- link with spacer fragments

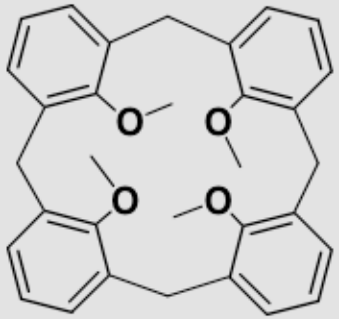
Step 3: Score the candidates

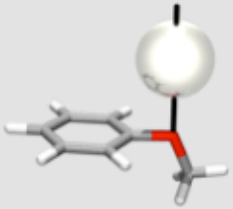
- LFER
- force field based methods

De novo structure-based host design?



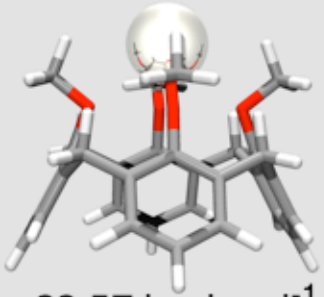
Use of electronic structure calculations



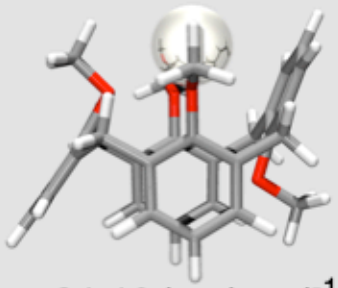


-14.4 kcal mol^{-1}

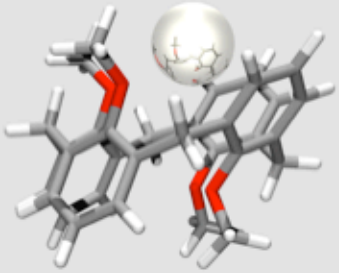
-13.8 kcal mol^{-1}



-22.57 kcal mol^{-1}



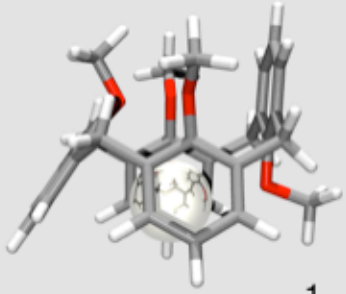
-31.10 kcal mol^{-1}



-33.98 kcal mol^{-1}

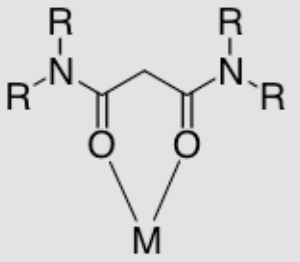
-35.14 kcal mol^{-1}

-37.07 kcal mol^{-1}



-41.65 kcal mol^{-1}

Understanding role of molecular structure gives basis for scoring



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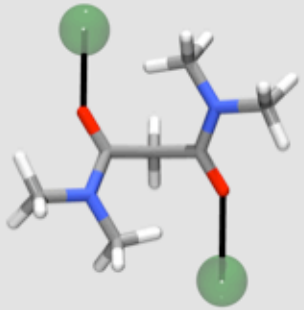

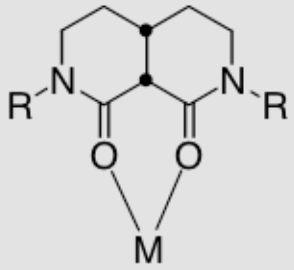

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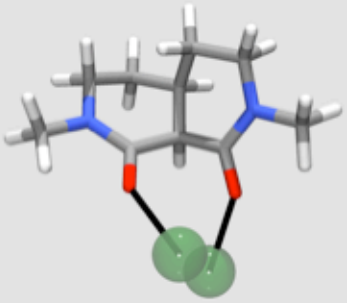
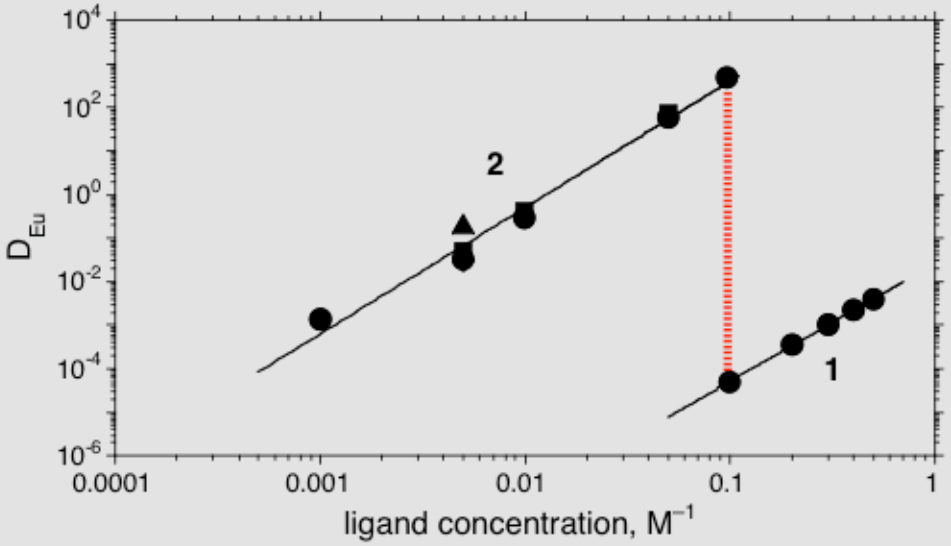


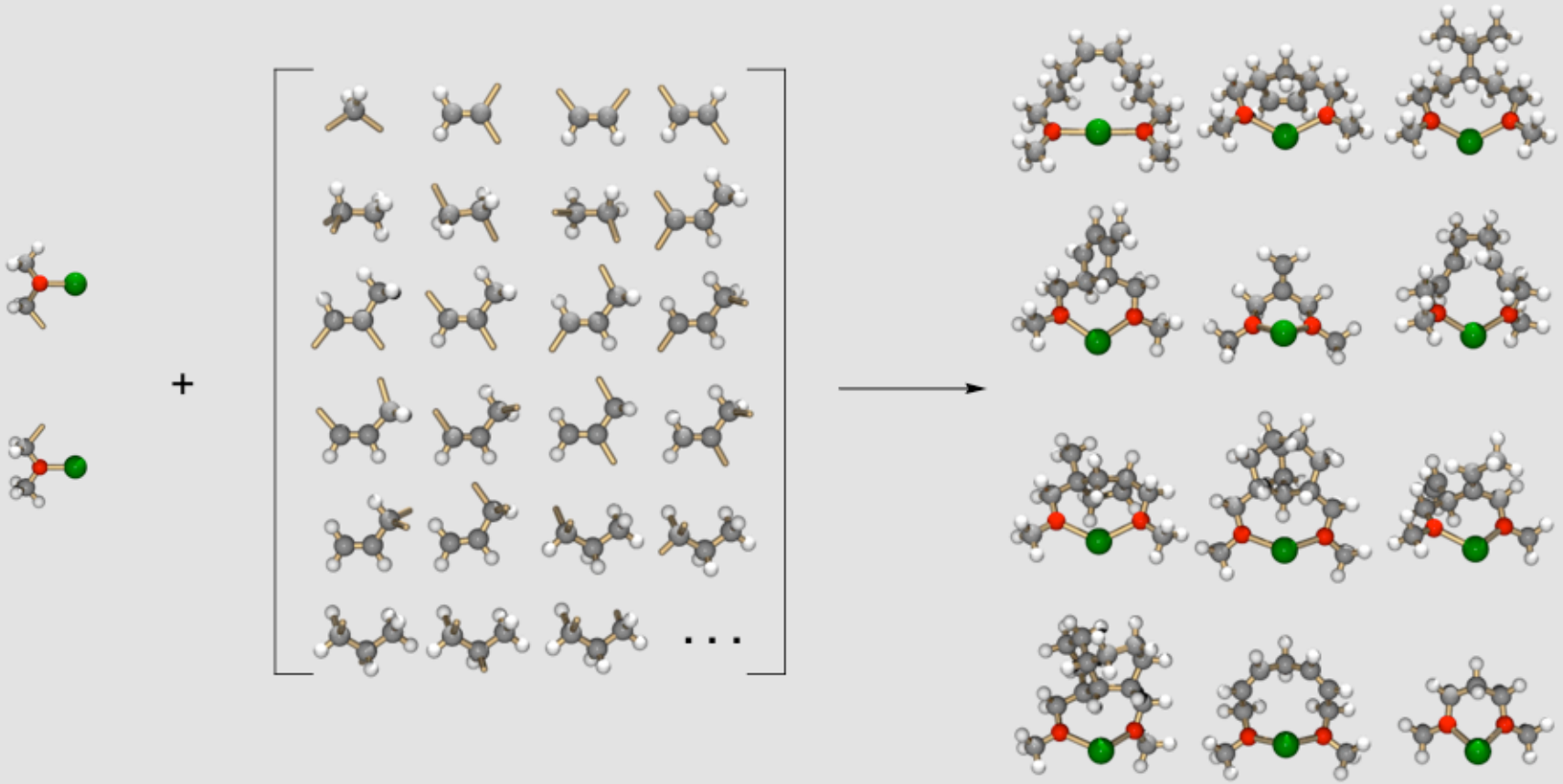
10 million times more effective



Extraction into t-butylbenzene from aqueous solution containing consisting of 1 M $NaNO_3$, 1.5 mM HNO_3, 0.1 mM $Eu(N0_3)_3$, and 1-µL of ^{155}Eu tracer solution.

J. Am. Chem. Soc. **2002**, *124*, 5644-5645

Structure generating software - HostDesigner

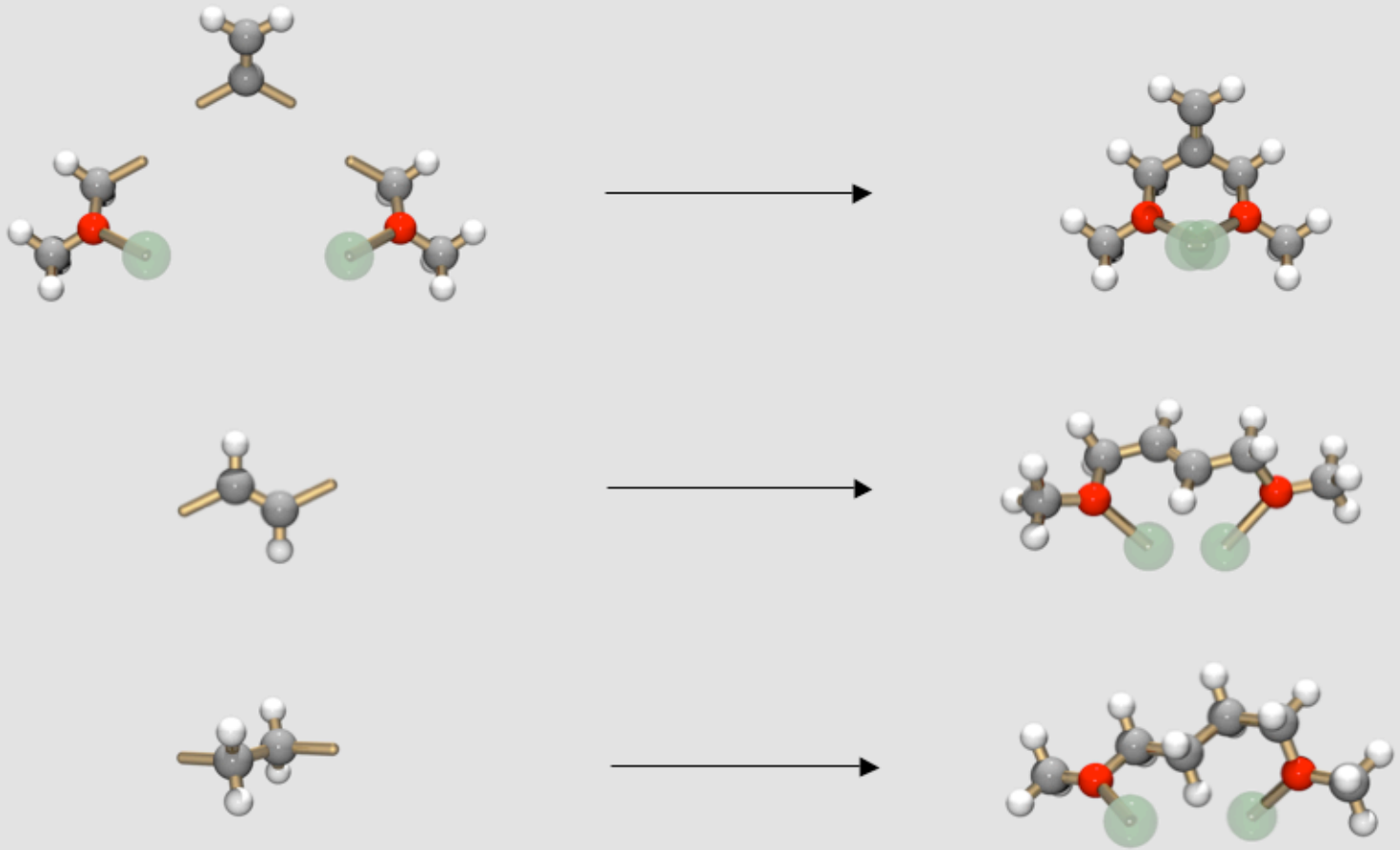


input fragments

fragment database 11,297 hydrocarbons

host structures

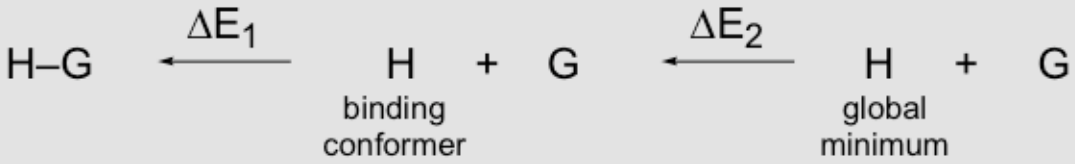
Initial scoring done by HD based on structure



Improved three-stage scoring process

Stage 1: Rank by degree of binding site convergence

143,985,540 geometries evaluated — 7 min, MacG5, 2 GHz



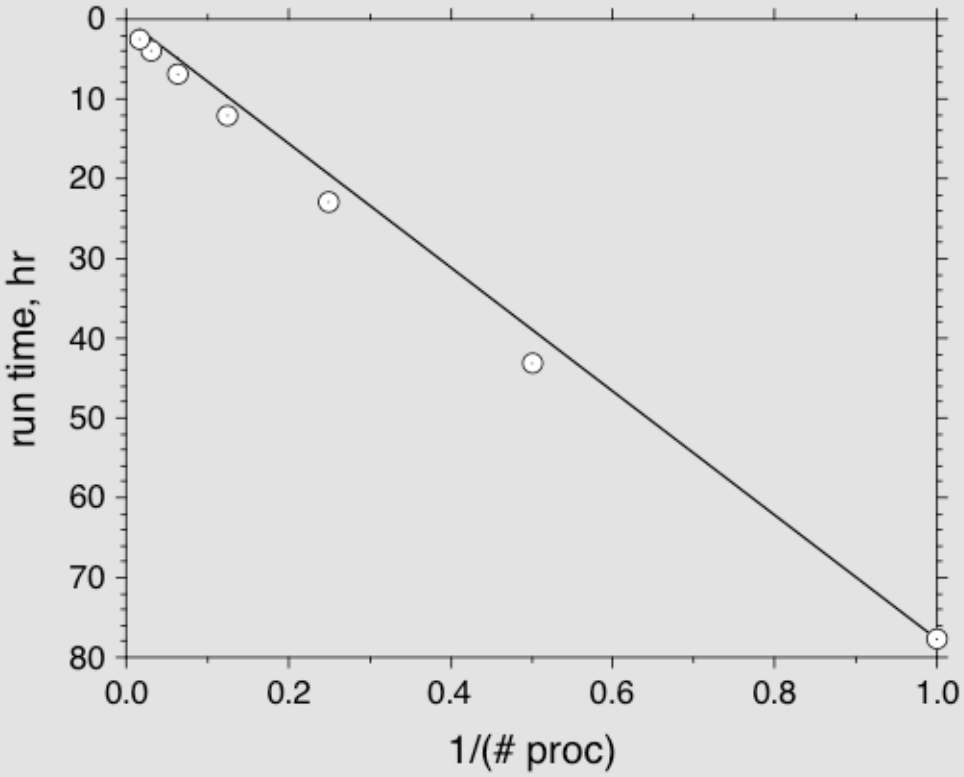
Stage 2: Rank by ΔE_1

5,000 binding energies — 80 min (0.5 sec/optimization)

Stage 3: Rank by $\Delta E_1 + \Delta E_2$

500 conformer searches — 76 hr (9.1 min/search)

Trivial parallelization (MPI) drops run times

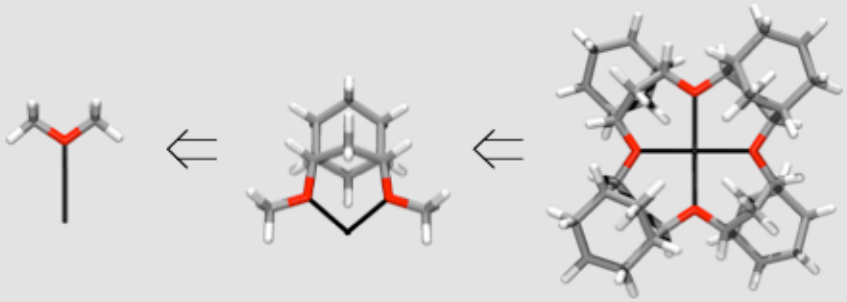


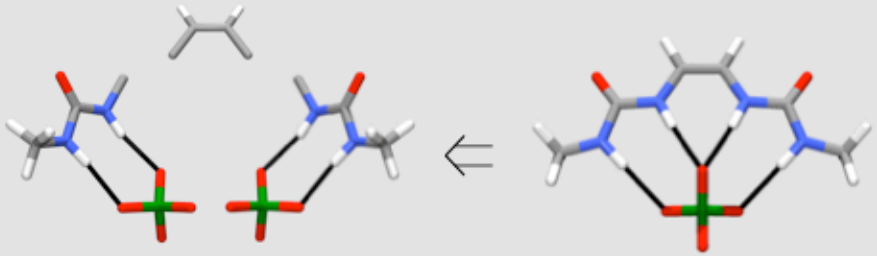
~ 2 hrs, 64 procs

78 hrs, 1 proc

(runs performed on mpp2 supercomputer, MSCF)

First two applications recently completed





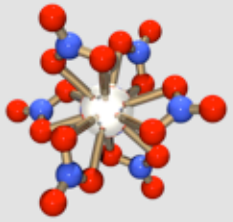
"Search for improved host architectures: Application of de novo structure-based design and high throughput screening methods to identify optimal building blocks for multidentate ethers"

Hay, B. P.; Oliferenko, A. A.; Uddin, J.; Zhang, C.; Firman, T. K. *J. Am. Chem. Soc.* **2005**, *127*, 17043-17053.

"De novo structure-based design of bis-urea hosts for tetrahedral oxoanion guests"

Bryantsev, V. S; Hay, B. P. *J. Am. Chem. Soc.* **2006**, *128*, 2035-2042.

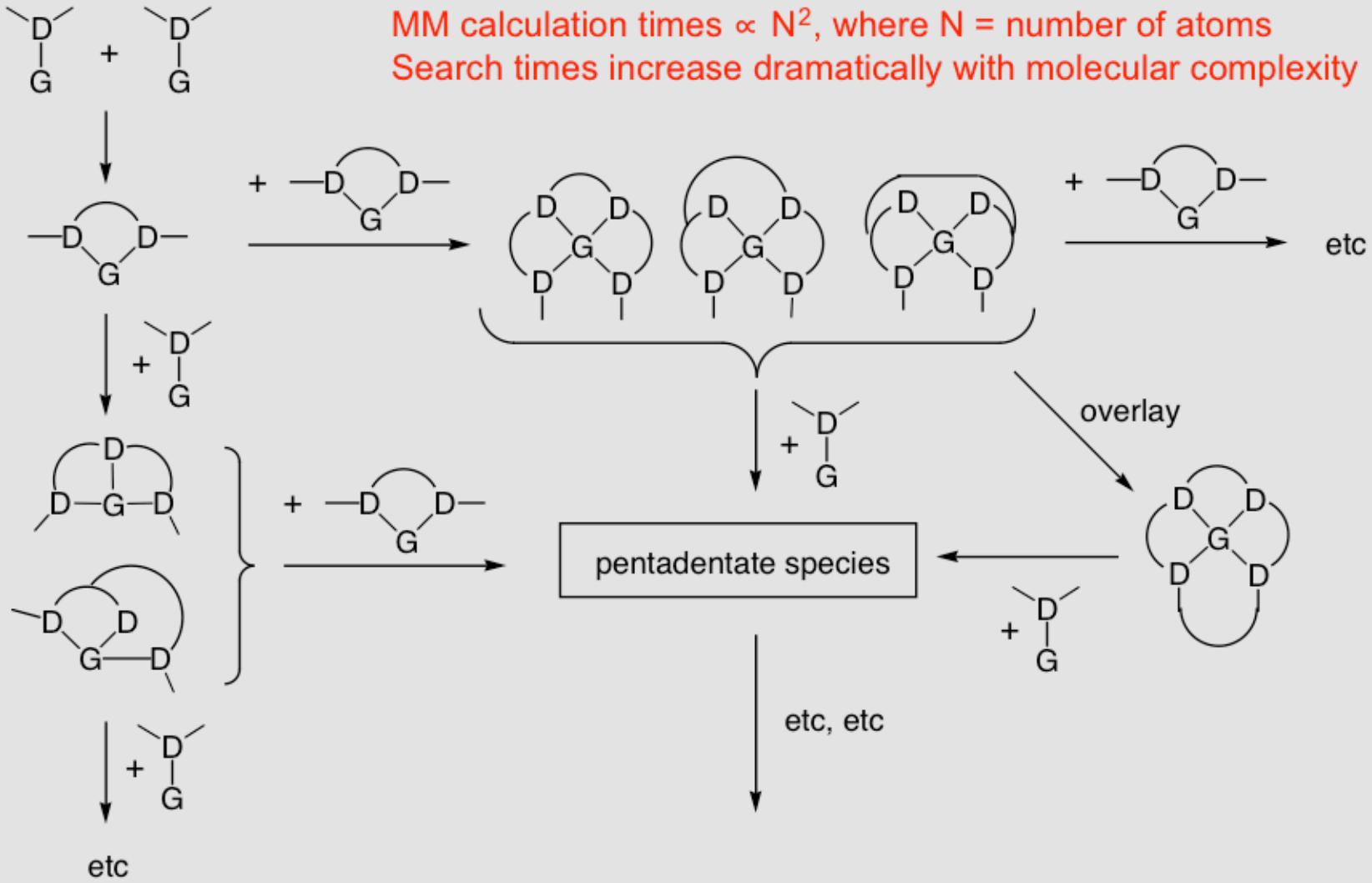
$[UO_2(NO_3)_3]^{-1}$



$[U(NO_3)_6]^{-2}$

Future applications will require larger computing resources

MM calculation times ∝ N^2, where N = number of atoms
Search times increase dramatically with molecular complexity



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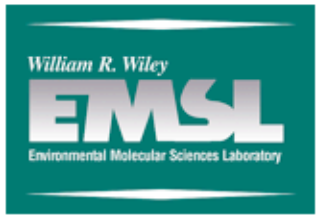

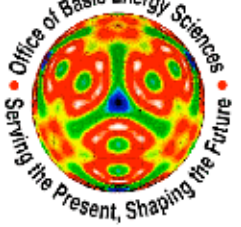

Structure-function and design research

PNNL
Slava S. Bryantsev (PD)
Dave Feller
Timothy K. Firman (PD)
Gregg J. Lumetta
Alex A. Oliferenko (PD)
Brian M. Rapko
Jamal Uddin (PD)
Rubi Vargas (PD)
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HostDesigner software

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Wibe A. de Jong
John B. Nicholas

Serena Software
Kevin E. Gilbert

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